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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/611,220	07/06/2000	Scott Arouh	90218	4817

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EXAMINER	
ALLEN, MARIANNE P	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 08/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/611,220	AROUH ET AL.	
	Examiner	Art Unit	
	Marianne P. Allen	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2004*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,14,15 and 27-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 14-15, 27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 5/21/04 has been entered.

Claims 10, 14-15 and 27-31 are pending and under consideration. Claims 27-31 have been newly introduced.

Information Disclosure Statement

Applicant is reminded of their duty to disclose information relevant to the invention and is encouraged to file an information disclosure statement.

Claim Rejections - 35 USC § 112

Claims 10, 14-15, and 27-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 10 has been substantively amended and claims 27-31 newly introduced. No basis has been pointed to for these amendments or new claims and none is apparent.

In particular, the specification does not appear to contemplate predicting optimal dosages of all thiopurine drugs with respect to cancer. Azothioprene does not appear to be disclosed. Mercaptopurine, azothioprene, thioguanine, and mixtures thereof are not disclosed as cancer drugs. TPMT is the name of a gene not an allele and the specification does not disclose any characteristic SNP patterns for this gene. (See new claims 29-31.)

Applicant is requested to point to page and line number of the specification in support of all claim amendments and newly introduced claims. See also rejections under 35 USC 112, second paragraph.

Claims 10, 14-15, and 27-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

Claim 10 is directed to a method of predicting a therapeutically optimal drug dosage or drug efficacy for a patient suffering from cancer. The method steps include 1) training a neural network to map (i) genomic data comprising alleles or characteristic SNP patterns to (ii) drug dosage results for a multiplicity of cancer patients (including

optimal drug dosages) and 2) exercising the trained constructed neural network on the genomic data of a particular patient to predict.

For the claims to be enabled, the specification, at the time the application was filed, must have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) discussed the factors to be considered in evaluating enablement. These factors include, but are not limited to, the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In the instant application the claims are broad. They are directed to a method of predicting a therapeutically optimal drug dosage or drug efficacy for a patient suffering from cancer. The claims embrace all cancers, all drugs, all alleles and characteristic SNP patterns (known or unknown) related to cancer.

The nature of the invention is complex. The claimed method requires finding a computationally manageable solution, if any, using neural network computer technology to solve a complex genomic data problem.

As reflected by the specification and art of record, the state of the art was such that those of ordinary skill in the art desired to predict a therapeutically optimal drug dosage or drug efficacy from genomic data. That is, they had identified a problem whose solution was of interest to those of ordinary skill in the art. However, no one had

successfully performed this method for any disease or drug, particularly those associated with cancer.

The level of skill in the art would have been high, yet the prior Office actions have documented the art's difficulty or inability to link allele/SNP patterns to disease at the time of the invention. Applicant's method goes beyond this task to then link allele/SNP patterns to optimal drug dosage to treat the particular disease.

The level of predictability in the art would have been low. That is, given the lack of success in the art at the time of the invention, one would not have been able to predict that one of ordinary skill in the art would have been able to practice the method as claimed.

The instant application provides no specific direction to particular cancers, drugs for treating cancer, no specific alleles and/or characteristic SNP patterns for any cancer. The instant application does not provide guidance as to what multiplicity of patients suffering from cancer to study. The instant application does not provide guidance as to what data to collect, how to organize or partition this data, how to analyze it, what assumptions to make, such that one of ordinary skill in the art would have been in a position to construct, train and exercise a neural network as set forth in the claims to make the required predictions.

The instant application provides no working examples of the claimed method.

The method as claimed would require a large quantity of experimentation to make or use the invention based on the content of the disclosure.

The specification does not identify alleles or characteristic SNP patterns for any or all cancers. Claim 10 requires knowledge or the determination of alleles and

characteristic SNP patterns to practice the method. The specification does not teach such alleles and characteristic SNP patterns for any cancer, particularly breast cancer. This is an invitation to experiment and constitutes undue experimentation. It would have required one of ordinary skill in the art to use inventive skill and judgment to develop the claimed method at the time of the invention.

Claim 15 further requires "training with the genetic algorithm continuing repetitively until...it becomes computationally possible to train the neural network to genomic data consisting of individual alleles or characteristic SNP patterns." This is an invitation to experiment and constitutes undue experimentation. It would have required one of ordinary skill in the art to use inventive skill and judgment to develop the claimed method at the time of the invention

The specification does not provide drug dosage results for a multiplicity of cancer patients nor optimal drug dosages. The specification does not reference any sources of such information. The specification does not provide any working examples of the method. The specification fails to provide guidance as to how to obtain the information required by the claimed method. As such, one would not be able to practice the claimed invention without undue experimentation.

The SBIR/STTR contract document previously submitted by applicant was dated well after the instant filing date. This document concerns the instant invention and acknowledges on page 5 that a great deal of software and data preparation had to be invented in order to successfully execute the method. Page 30 documents that the biggest hurdle was obtaining the patient data source and that cost prevented the inventors for generating a patient pool designed for the study.

Applicant is reminded that the method under examination requires drug treatment dosages and genomic data for the patients. Identity of the drug alone would not be sufficient. It is maintained that the patient information required to train the neural network would not have been well known and readily available at the time of the invention.

Applicant is reminded that experimentation that requires ingenuity beyond that to be expected of one of ordinary skill in the art is considered undue. See Fields v. Conover, 170 USPQ 276. That is, one of ordinary skill in the art would have been required to adapt known genomic data and drug dosage data (select, compile, format, etc.) or generate the genomic data and drug dosage data required by the claims. Then one of ordinary skill in the art would have been required to decide how to use this data and develop the required neural network.

It is further noted that the SBIR/STTR contract document investigated a known pathway with known genomic markers and known drugs for treatment. One of ordinary skill in the art would have had to practice undue experimentation to train, validate, and test a neural network for such data. The analysis and judgment required to do this would not have been routine but have required inventive skill beyond the limited guidance provided by the application. The computational complexity of such a situation would be significantly greater than what this document exemplifies. Note that the application itself provides no exemplification at all.

The Schork affidavit under 37 CFR 1.132 filed 3/25/03 is insufficient to overcome this rejection. It is noted that the references cited in the affidavit were not provided and are not of record in the instant application. The affidavit discusses the

cytochrome P450 gene family. The claims are not directed to this gene family nor diseases specifically associated with this gene family nor drugs known to be differentially metabolized by the cytochrome P450 system. The affidavit does not speak to predicting a therapeutically optimal drug dosage or drug efficacy for a particular individual suffering from cancer using a neural network based upon the disclosure of the specification. In fact, the affidavit directs one to pick a drug, review the literature to determine if a gene target (or set of genes) is known for the drug with respect to its pharmacodynamic aspects, determine if variations in genes exist, and identify individuals who have been treated with relevant drugs and genotype them. See paragraphs 30-36 of the affidavit. All of these steps require judgment and decision making on the part of the person practicing these steps. This is undue experimentation. Note that unlike paragraph 31, the claims do not require identifying a set of genes based on pharmacodynamic aspects of the drug. Note that the affidavit doesn't explain how these individuals who have been treated with relevant drugs will be located and how one of ordinary skill in the art would be in a position to obtain their genotypes. In fact, paragraph 39 assumes that human subjects will be available to most practitioners and that it is routine medical practice to catalog drugs and dosages. It is not agreed that one of ordinary skill in the art would have access to such human subjects and/or their medical records. Clinical studies require informed consent and patient confidentiality. This data is not publicly known nor freely available. Access to such data is restricted. Again, the SBIR/STTR contract document on page 30 documents that the biggest hurdle was obtaining the patient data source and that cost prevented the inventors for generating a patient pool designed for the study. In addition, there is no discussion of determining optimal drug dosages nor any of

the other information required by claim 10. Availability of a database of genetic variability does not provide a relationship between an allele or characteristic SNP pattern and any cancer. It does not speak to optimal drug dosage or drug efficacy. See paragraphs 41-44 of the affidavit.

The claims are not enabled.

Claims 10, 14-15, and 27-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is confusing in reciting "suffering from cancer in respect of genomic data." It is unclear what is intended by this phrase.

Claim 10 is confusing in reciting "characteristic SNP patterns." It is not known what defines a characteristic SNP pattern or what type of SNP pattern is required to meet this limitation.

Claim 10 requires alleles or characteristic SNP patterns for locations and types of introns, ethnicity, race, diet type, home region, occupation, viral levels, peptide levels, blood plasma levels, pharmacokinetic and pharmacodynamic parameters, and combinations thereof. It is not known what alleles or SNP patterns define these attributes. For example, what is the characteristic SNP pattern that defines a vegetarian or that defines someone who lives in Minnesota or that defines a blood plasma level of X?

Claim 10 also requires alleles or characteristic SNP patterns for "entire gene families." It is not known what defines an entire gene family. What are the criteria for inclusion or exclusion in a particular family?

Claim 10 is confusing in reciting "historical drug dosage results are related to at least some of the genomic data so as to make a trained neural network that is fit." It is not known what degree of relatedness is required to meet the limitation of the claim. It is not known what specific criteria would meet the limitation of "fit." Furthermore, the genomic data comprising alleles or characteristic SNP patterns in lines 7-8 and lines 24-30 (newly introduced) of claim 10 is not clearly required to be related to cancer or the same cancer as the historical drug dosage results.

The preamble of claim 10 is directed to both predicting a therapeutically optimal drug dosage and predicting drug efficacy. However, the body of the claim does not address predicting drug efficacy.

Claim 10 recites that historical drug dosage results are selected from a particular group of conditions. (See last 8 lines of the claim as newly amended.) This is confusing as this portion of the claim is not addressing the multiplicity of patients referred to previously in the claim. In particular, why are "cost or performance functions calculated from values of multiple 'real' clinical variables" considered historical drug dosage results? What is intended by the term "real"? Why is the "presence of any of biological conditions, diseases, and characteristics" considered historical drug dosage results? What constitutes a "characteristic"?

In particular, claims 10 and 28 are confusing in reciting "any presence of characteristics for which a genetic or environmental origin is either not clear or not

uniquely defined." It is not known what is required to meet the limitation of the claim. What level of clarity or unique definition is necessary?

Claim 15 requires grouping alleles or characteristic SNP patterns into families defined as "having similar expression patterns" or "being turned on and off by another gene" or both. It is not known what level of similarity would be required for such grouping. It is not known which SNP patterns are turned on and off by another gene. (It is unclear if this must be the same gene or could be different genes.) It doesn't appear that the SNP or allele are turned on or off but rather some particular gene that is expressed.

Claim 29 is confusing because TPMT is not an allele.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Thursday, 5:30 am - 1:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne P. Allen

Marianne P. Allen
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mpa